CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022516Orig1s000

OTHER REVIEW(S)

REGULATORY PROJECT MANAGER LABELING REVIEW

Division of Anesthesia and Analgesia Products

Application Number: NDA 22-516

Name of Drug: Cymbalta (duloxetine hydrochloride) Capsules

Applicant: Eli Lilly and Company

Material Reviewed:

Submission Date(s): May 15, 2009, and October 14, 2010

Receipt Date(s): May 15, 2009, and October, 14, 2010

Submission Date of Structure Product Labeling (SPL): NA

Type of Labeling Reviewed: WORD

Reviews Completed: Ayanna Augustus, Ph.D., RPM
Parinda Jani, CPMS

Background and Summary

NDA 22-516 is a Type 6 NDA to expand the indication for Cymbalta for the management of chronic musculoskeletal pain. NDA 21-427 for Cymbalta is currently approved for the treatment of Major Depressive Disorder (MDD), General Anxiety Disorder (GAD), Diabetic Peripheral Neuropathic Pain (DPNP) and Fibromyalgia (FM).

The sponsor also submitted to NDA 21-427, labeling supplement S-033, which proposed changes to:

- **ADVERSE REACTIONS: Adverse Reactions Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials**

- **CLINICAL STUDIES: Fibromyalgia**

These changes were also incorporated into the labeling for NDA 22516. The revised labeling submitted by the sponsor on October 14, 2010, was compared to the labeling approved by DPP on November 19, 2009 (NDA 21-427/S-030).

Review

Please note that the sponsor's proposed omissions are indicated by strikeovers, inclusions by

underlined text.

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[redacted]

MEDICATION GUIDE: No changes noted.

Recommendations

This supplement is recommended for approval.

Ayanna Augustus, Ph.D.
Regulatory Project Manager

Supervisory Comment/Concurrence:

Parinda Jani
Chief, Project Management Staff

Drafted: AA/10/19/10
Revised/Initialed:
Finalized:
Filename: CSO Labeling Review Template (updated 1-16-07).doc

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/s/

AYANNA S AUGUSTUS
11/03/2010

PARINDA JANI
11/04/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	July 19, 2010
To:	Bob Rappaport, M.D., Director Division of Anesthesia and Analgesia Products (DAAP) Office of New Drugs (OND)
Through:	Mark Avigan, M.D., C.M., Director Division of Pharmacovigilance (DPV I) and Ida-Lina Diak, Pharm.D., Safety Evaluator Team Leader Division of Pharmacovigilance (DPV I)
From:	Laurelle Cascio, Pharm.D., Safety Evaluator Division of Pharmacovigilance (DPV I)
Subject:	Updated Safety Profile
Drug Name(s):	Duloxetine
Application Type/Number:	NDA 21427, NDA 21733, NDA 22148
Applicant/sponsor:	Eli Lilly
OSE RCM #:	2010-1208

CONTENTS

EXECUTIVE SUMMARY

In preparation for an upcoming Advisory Committee (AC) meeting, the Division of Anesthesia and Analgesia Products (DAAP) requested that the Division of Pharmacovigilance (DPV) provide a summary document of the safety profile for duloxetine. This review incorporates safety data from both the premarketing and postmarketing phases of drug development. The information gathered from a New Molecular Entity (NME) Postmarketing Safety Evaluation conducted on 13 March 2007 was consistent with the recent FDAAA requirement for FDA to review the safety profiles of all new drugs[1]. This was a collaborative effort, primarily conducted by two offices within FDA, to assess safety concerns listed in the product labeling and postmarketing information gathered from spontaneous reports, epidemiological data, and literature findings.

OSE determined that most of the postmarketing safety findings were reflected in the product label. A few findings led OSE to perform thorough analyses of AERS cases of urinary retention/hesitation, bleeding disorders, Steven-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN), and serious liver injury. Each of these new safety reviews led to subsequent modifications to the duloxetine label, with the exception of TEN.

At the time of the NME evaluation in 2007, DPV provided the top 50 adverse event preferred terms (PT) reported with duloxetine from the approval date in 2004 through 28 February 2007. At that time, the only terms identified as unlabeled events were “fall”, “dyspnoea”, and “chest pain”. For the purpose of this update, we repeated a search in the AERS database to retrieve the top 50 adverse events reported with duloxetine since the NME evaluation, date of output 28 February 2007, through 11 June 2010. Since 2007, many of the updated adverse event terms were found to be a duplication of the terms found in the NME evaluation. In our updated search, the term “chest pain” was not one the top PTs reported, as it was in the NME evaluation. In contrast, the terms “fall” and “dyspnoea” have continued to be reported in AERS as two of the top 50 PTs. The risk of falls is currently reflected in the duloxetine label. The reported event “dyspnoea” has not been considered as a potential safety signal at this time.

DPV recommends that the duloxetine safety profile reflected in the current product label be considered as part of an overall assessment of the benefit-risk of this product for the newly proposed indication of chronic pain.

1 INTRODUCTION

In preparation for an upcoming AC meeting, DAAP requested that DPV provide a summary document of the safety profile for duloxetine. This review provides an update of safety information since the NME Postmarketing Evaluation was performed on 13 March 2007.[1]

1.1 REGULATORY HISTORY

Cymbalta® (duloxetine hydrochloride) is a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) for oral administration. Although the exact mechanisms of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, these actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the central nervous system (CNS).[2]

Table 1. Summary of the approved indications for duloxetine

Indication	Approval Date
Major Depressive Disorder (MDD)	August 3, 2004
Generalized Anxiety Disorder (GAD)	November 19, 2009
Diabetic Peripheral Neuropathic Pain (DPNP)	September 3, 2004
Fibromyalgia (FM)	June 13, 2008

1.2 IMPORTANT SAFETY EFFECTS OF DULOXETINE CAPTURED IN THE CURRENT PRODUCT LABELING

***Safety Effects Captured in the CONTRAINDICATIONS Section*:**[2]

- Use of a monoamine oxidase inhibitor concomitantly or in close temporal proximity
- Use in patients with uncontrolled narrow-angle glaucoma

***Safety Effects Captured in the WARNINGS AND PRECAUTIONS Section*:**[2]

- Suicidality: Monitor for clinical worsening and suicide risk
- Hepatotoxicity: Hepatic failure, sometimes fatal, has been reported in patients treated with Cymbalta. Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established. Cymbalta should ordinarily not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease
- Orthostatic Hypotension and Syncope: Cases have been reported with duloxetine therapy.
- Serotonin Syndrome, or Neuroleptic Malignant Syndrome (NMS)-like reactions: Serotonin syndrome or NMS-like reactions have been reported with SSRIs and SNRIs. Discontinue Cymbalta and initiate supportive treatment.
- Abnormal Bleeding: Cymbalta may increase the risk of bleeding events. Patients should be cautioned about the risk of bleeding associated with the concomitant use of duloxetine and NSAIDs, aspirin, or other drugs that affect coagulation.
- Discontinuation: May result in symptoms, including dizziness, nausea, headache, fatigue, paresthesia, vomiting, irritability, nightmares, insomnia, diarrhea, anxiety, hyperhidrosis, and vertigo
- Activation of mania or hypomania has occurred
- Seizures: Prescribe with care in patients with a history of seizure disorder

- Blood Pressure: Monitor blood pressure prior to initiating treatment and periodically throughout treatment
- Inhibitors of CYP1A2 or Thioridazine: Should not administer with Cymbalta
- Hyponatremia: Cases of hyponatremia have been reported
- Hepatic Insufficiency and Severe Renal Impairment: Should ordinarily not be administered to these patients
- Controlled Narrow-Angle Glaucoma: Use cautiously in these patients
- Glucose Control in Diabetes: In diabetic peripheral neuropathic pain patients, small increases in fasting blood glucose, HbA1c, and total cholesterol have been observed
- Conditions that Slow Gastric Emptying: Use cautiously in these patients
- Urinary Hesitation and Retention

***Safety Effects Captured in the ADVERSE REACTIONS Section*:**[2]

- Most common adverse reactions (≥5% and at least twice the incidence of placebo patients): nausea, dry mouth, constipation, somnolence, hyperhidrosis, and decreased appetite

***Safety Effects Captured in the DRUG INTERACTIONS Section*:**[2]

- Potent inhibitors of CYP1A2 should be avoided
- Potent inhibitors of CYP2D6 may increase duloxetine concentrations
- Duloxetine is a moderate inhibitor of CYP2D6

1.3 PREVIOUS DPV REVIEWS

On 13 March 2007 reviewers from the Office of Surveillance and Epidemiology (OSE) and the Office of Drug Evaluation I (ODE I) within FDA's Center for Drug Evaluation and Research (CDER) presented an overview of their safety data for duloxetine as part of the New Molecular Entity (NME) Postmarketing Safety Evaluation Pilot Program. The evaluation was a systematic, collaborative process which involved a review of potential safety concerns identified for duloxetine since its approval by the FDA. Data presented during this meeting included information on adverse events in the Adverse Event Reporting System (AERS) database, a data mining analysis of AERS data, a literature review, a medication error analysis, and a discussion of postmarketing clinical trial findings. The surveillance procedure identified some previously unrecognized safety issues and provided more information about some previously known safety issues for duloxetine[3]. New safety signals requiring further investigation and analysis were thoroughly discussed between the two offices.[1] Findings of the NME evaluation that were considered necessary for further review are summarized in section 1.3.1, 1.3.2, and 1.3.3 below, as well as thorough safety reviews completed by OSE since the completion of the evaluation. These evaluations are included in the background material provided with this document.

1.3.1 New Molecular Entity (NME) Postmarketing Evaluation

On 8 May 2007 the Duloxetine NME Review team completed a postmarketing safety screening evaluation of duloxetine to identify safety issues that were considered necessary for further review.[3] The major findings of this evaluation spanned multiple postmarketing data streams. Five potential new safety signals prompted further assessment; blindness, falls/loss of consciousness, bleeding disorders, urinary hesitancy, and drug interactions. A plan to perform a series of thorough reviews for these events, utilizing the AERS database, was undertaken.

As a result of the evaluation, the following action items were carried out:

The AERS cases of "blindness" were deemed to be unrelated to the use of duloxetine; however, the adverse event appeared to instead, be related to the underlying disease or other causes. It was also felt that the "risk of falls" was appropriately reflected in the current labeling and that "loss of consciousness' is an event associated with multiple possible causes that are currently listed in labeling, thus further review of these events were not undertaken.

A signal of "drug interactions" was considered for further review by DPV, although no continued action was taken since it was determined that many of the drug interactions were explained by the drug information provided in the duloxetine label. In addition, DPV identified reports describing a potential interaction between duloxetine and warfarin and determined that the interaction was appropriately labeled in the "Drug Interaction" section of the duloxetine label.

In contrast, AERS signals of "urinary retention/hesitancy" and "bleeding disorders" were fully reviewed by DPV through analysis of case series developed for each of these events. A summary of the review findings can be found in sections 1.3.2 and 1.3.3. In 2008, OSE also performed full AERS reviews of "SJS/TEN" and "serious liver injury", which are summarized in sections 1.3.4 and 1.3.5.

1.3.2 Urinary Retention/Hesitation

DPV completed a full safety review dated 11 July 2007, which evaluated postmarketing reports of urinary retention and urinary hesitation associated with duloxetine.[4]

OSE recommended adding "urinary retention that resulted in hospitalization and, or catheterization as seen in postmarketing cases" to the Precautions section of duloxetine label.

Prior to this review, labeling about urinary retention or hesitation was included in the "Adverse Reaction" section of duloxetine. In the November 2007 label revision, information about urinary retention requiring hospitalization and/or catheterization associated with duloxetine use was added to the "Postmarketing" section.

1.3.3 Bleeding

DPV completed a full safety review on 18 September 2007, which evaluated postmarketing reports of bleeding events with duloxetine.[5]

DPV recommended the following:

- Adding the "Abnormal Bleeding" statement in the "Precaution" section of the SSRI labels to the duloxetine label
    - "SSRIs and SNRIs may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to the risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages."[6]
- Adding the drug interaction language for warfarin and drugs that affect hemostasis (ASA, NSAIDS, and anticoagulants) found in the SSRI labels to the duloxetine label

- Adding patient information language regarding concomitant use of ASA, NSAIDs, or anticoagulants found in the SSRI labels to the duloxetine label.

Prior to this review, labeling about the risk of bleeding was not included in the label for duloxetine. In the November 2007 label revision, all DPV proposed label changes to reflect the risk of bleeding with duloxetine were added to the "Warnings and Precautions", "Drug Interactions", and "Patient Counseling Information" sections.

1.3.4 SJS, TEN

DPV completed a full safety review on 6 August 2008, which evaluated postmarketing reports of serious skin disorders SJS and TEN among the SSRIs and SNRIs and compared the reporting rates across products.[7]

OSE recommended elevating the current serious skin labeling to the "Warnings and Precautions" section and adding language about the fatality potential with SJS/TEN to the "Postmarketing" section of the duloxetine label.

Prior to this review, the labeling for serious skin reactions for duloxetine stated "serious skin reactions including Stevens-Johnson Syndrome that have required drug discontinuation and/or hospitalization have been reported with duloxetine", and to date, no current labeling changes have been made as a result of this review.

1.3.5 Serious Liver Injury

In addition to the previous OSE reviews regarding the potential liver toxicity for duloxetine, DPV completed a full review on 20 August 2008, which evaluated postmarketing reports of serious liver injury associated with the SNRIs duloxetine, desvenlafaxine, and venlafaxine.[8]

The review stated that hepatotoxicity associated with duloxetine therapy was recognized and labeled in the "Warning and Precautions" section.

DPV recommended that the "sponsor use 15-day reporting of all elevated transaminase levels with elevated bilirubin levels, clinical jaundice or any suggestion of serious liver injury; sponsor monitor for liver toxicity and actively pursue follow-up for any reports of elevated transaminase levels with elevated bilirubin levels, clinical jaundice or any indication of serious liver injury; and add labeling in the "Information for Patients" section and the Medication Guide to instruct patients to discontinue duloxetine and contact their primary care physician if they experience dark urine or a yellow discoloration of the eyes, inside the mouth, or skin."

At that time, DPP felt that the potential for liver toxicity was appropriately reflected in the current labeling.

2 METHODS AND MATERIALS

2.1 AERS DATABASE

We conducted a thorough search in the AERS database to retrieve all adverse event reports associated with duloxetine from 28 February 2007 to 11 June 2010. Drug terms we searched were duloxetine and Cymbalta®.

3 RESULTS

3.1 ADVERSE EVENTS CASES

Table 1 provides a list of the top 50 MedDRA preferred terms from the AERS database since the NME Postmarketing Evaluation, from 28 February 2007 to 11 June 2010. The following adverse events are sorted by decreasing number.

Table 1. AERS Crude Counts of the Top 50 Preferred Term Adverse Events from 28 February 2007 to 11 June 2010

Key: BB=Black Box Warning DA=Dosage and Administration WP=Warnings and Precautions AR=Adverse Reactions CI=Contraindications MG=Medication Guide SP=Use in Specific Populations PCI=Patient Counseling Information OD=Overdose BP=Blood Pressure

Rank	Preferred Term	Count of PTs	% of Total	Label Status	Label Location	Term(s) Used In Label	Comments
1	Nausea	685	9.85	Labeled	AR, WP		
2	Dizziness	643	9.25	Labeled	WP,A/R,PCI		
3	Headache	457	6.57	Labeled	WP, AR		
4	Drug Withdrawal Syndrome	442	6.36	Labeled	DA,WP,SP	Discontinuation, discontinuation syndrome	
5	Feeling Abnormal	371	5.34	Labeled	AR		
6	Paraesthesia	369	5.31	Labeled	AR		
7	Insomnia	363	5.22	Labeled	WP,AR,PCI,MG		
8	Fatigue	354	5.09	Labeled	WP,AR		
9	Depression	328	4.72	Labeled	WP,PCI,MG		
10	Suicidal Ideation	318	4.57	Labeled	BB,WP, AR,MG, PCI	Suicidal ideation, suicidal thinking, suicidality, suicide risk	
11	Vomiting	303	4.36	Labeled	WP,OD, AR, SP		
12	Anxiety	293	4.22	Labeled	AR,WP, PCI,MG		
13	Alanine Aminotransferase Increased	287	4.13	Labeled	WP	Elevation of transaminase levels, ALT elevation	

Rank	Preferred Term	Count of PTs	% of Total	Label Status	Label Location	Term(s) Used In Label	Comments
14	Completed Suicide	286	4.11	Labeled	AR		
15	Hyperhidrosis	277	3.99	Labeled	WP,AR		
16	Hepatic Enzyme Increased	274	3.94	Labeled	WP	Elevation of transaminase levels, ALT and AST elevation	
17	Drug Ineffective	272	3.91	----------			
18	Drug Interaction	272	3.91	Labeled	DI		Label contains "Drug Interaction" section which includes information about CYP1A2 and CYP2D6 being responsible for duloxetine metabolism.
19	Tremor	265	3.81	Labeled	AR,SP		
20	Pain	254	3.65	Labeled	AR	Abdominal pain, ear pain, pharyngolaryngeal pain, musculoskeletal pain	
21	Aspartate Aminotransferase Increased	243	3.5	Labeled	WP	Elevation of transaminase levels, AST elevation	
22	Malaise	235	3.38	Labeled	AR		
23	Diarrhoea	232	3.34	Labeled	WP, AR		
24	Fall	232	3.34	Labeled	WP,AR, OD, PCI	Falls, somnolence, sedation and dizziness	Associated with hyponatremia; somnolence, sedation and dizziness may lead to falls.
25	Somnolence	225	3.24	Labeled	AR, OD		
26	Loss Of Consciousness	223	3.21	Labeled	WP, OD, CI	Coma	Associated with hyponatremia; in overdose situations; concomitant use with MAOIs; serotonin syndrome
27	Weight Increased	202	2.91	Labeled	AR		

Rank	Preferred Term	Count of PTs	% of Total	Label Status	Label Location	Term(s) Used In Label	Comments
28	Suicide Attempt	192	2.76	Labeled	BB,AR,WP	Suicide attempt, suicidality	
29	Crying	178	2.56	Labeled	SP	Constant crying	Labeled for infants, also can be associated with the underlying disease of depression, for which duloxetine is indicated as treatment
30	Blood Pressure Increased	176	2.53	Labeled	WP,AR,OD	Hypertension, ↑ in mean BP, mean ↑ in systolic BP, mean ↑ in diastolic BP, ↑ in supine BP	
31	Confusional State	173	2.49	Labeled	WP,AR	Confusional state, confusion	
32	Hypertension	166	2.39	Labeled	WP,AR,OD	Hypertension, ↑ in mean BP, mean ↑ in systolic BP, mean ↑ in diastolic BP, ↑ in supine BP	
33	Irritability	165	2.37	Labeled	WP, AR, SP, PC		
34	Withdrawal Syndrome	163	2.34	Labeled	DA,WP, SP	Discontinuation, discontinuation syndrome	
35	Asthenia	161	2.32	Labeled	AR		
36	Decreased Appetite	159	2.29	Labeled	AR		
37	Drug Exposure During Pregnancy	157	2.26	Labeled	SP		Label states the risks associated with neonates exposed to duloxetine during third trimester of pregnancy; discusses weighing risk versus benefit to justify using duloxetine during pregnancy.

Rank	Preferred Term	Count of PTs	% of Total	Label Status	Label Location	Term(s) Used In Label	Comments
38	Liver Function Test Abnormal	153	2.2	Labeled	WP	Elevation of transaminase levels, liver transaminase elevations	
39	Agitation	152	2.19	Labeled	CI,WP,AR,PCI		
40	Convulsion	152	2.19	Labeled	WP, AR, SP, OD	Seizures, convulsions	
41	Death	146	2.1	Labeled	WP	Sudden death, Death	Sudden death associated with concomitant use with thioridazine; death associated with hyponatremia
42	Disturbance In Attention	144	2.07	Labeled	AR		
43	***Dyspnoea***	143	2.06	***Not Labeled***			
44	Anger	139	2	Labeled	AR		
45	Vision Blurred	139	2	Labeled	AR		
46	Hospitalisation	135	1.94	Labeled	WP,AR,SP		Associated with urinary retention; complications in neonate when drug used in third trimester of pregnancy
47	Nightmare	135	1.94	Labeled	WP,AR		
48	Weight Decreased	130	1.87	Labeled	AR	Weight changes, weight decreased	
49	Palpitations	129	1.86	Labeled	AR		
50	Abnormal Behaviour	128	1.84	Labeled	BB,WP,PCI	Unusual changes in behavior, suicidal thinking and behavior	

4 DISCUSSION

Duloxetine's safety issues have been extensively reviewed by both OND and OSE reviewers, as recognized by the NME Postmarketing Evaluation dated 13 March 2007[1]. Since that time, potential safety issues were reviewed by OSE, which included urinary retention/hesitation, bleeding disorders, Steven-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN), and serious liver injury. The current labeling of duloxetine now reflects the risks for urinary hesitation and retention (warnings and precautions), bleeding abnormalities (warnings and precautions), SJS requiring hospitalization (postmarketing section), and liver toxicity (warnings and precautions).

For the purpose of this review, we provide an update of the top 50 adverse event terms reported for duloxetine since the NME evaluation in 2007. Many of the updated adverse event terms are found to be a duplication of the terms found in the NME evaluation. Our primary focus was to compare previously unlabeled adverse events identified in the NME evaluation with unlabeled adverse events reported in AERS. In our updated search, the term "chest pain" was not one the top PTs reported, as it was in the NME evaluation. In contrast, the terms "fall" and "dyspnoea" have continued to be reported in AERS as two of the top 50 PTs. The risk of falls is currently reflected in the duloxetine label. The reported event "dyspnoea" has not been considered as a potential safety signal at this time.

5 CONCLUSION

There are a series of known safety effects of duloxetine enunciated in the product label. Recently, the risk of urinary retention/hesitation, bleeding, SJS, serious liver injury, , and falls/loss of consciousness have been added. The current product label appears to reflect our current understanding of the safety profile of duloxetine.

6 RECOMMENDATIONS

DPV recommends that the duloxetine safety profile reflected in the product label be considered as part of an overall assessment of the benefit-risk of this product for the newly proposed indication of chronic pain.

7 REFERENCES

1. FDA U.S. Food and Drug Administration. New Molecular Entity Postmarketing Safety Evaluation Pilot Program Final Report. Accessed 30 June 2010. <http://www fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103457 htm.
2. Cymbalta® (Duloxetine) [package insert] Indianapolis, IN: Eli Lilly and Company. November 2009.
3. FDA, 2007, Center for Drug Evaluation and Research (CDER). New Molecular Entity (NME) Postmarketing Evaluation, 13 March 2007.
4. Lyndly J. FDA Post-marketing safety review: Urinary Retention and Urinary Hesitation; NME Review Follow-up, 11 July 2007.
5. Lyndly J. FDA Post-marketing safety review: Bleeding; NME Review Follow-up, 18 September 2007.
6. Celexa® (Citalopram) [package insert] St. Louis, MO: Forest Pharmaceuticals. January 2009.
7. La Grenade L et al. FDA Post-marketing safety review: Stevens-Johnson Syndrome (SJS) & Toxic epidermal Necrolysis (TEN), 6 August 2008.
8. Lyndly J et al. FDA Post-marketing safety review: Serious Liver Injury (SLI), 20 August 2008.

8 APPENDICES

8.1 APPENDIX A. NME POSTMARKETING EVALUATION OF AERS CRUDE COUNTS OF THE TOP 50 ADVERSE EVENTS FROM APPROVAL TO 28 FEBRUARY 2007

Rank	Preferred Term	Count of PTs	Percent of Total	Label Status
1	Nausea	724	11.16	Labeled
2	Feeling Abnormal	509	7.84	Labeled
3	Dizziness	482	7.43	Labeled
4	Insomnia	392	6.04	Labeled
5	Fatigue	368	5.67	Labeled
6	Headache	348	5.36	Labeled
7	Blood Pressure Increased	312	4.81	Labeled
8	Somnolence	310	4.78	Labeled
9	Depression	300	4.62	Labeled
10	Drug Ineffective	282	4.35	---------
11	Anxiety	262	4.04	Labeled
12	Hyperhidrosis	261	4.02	Labeled
13	Tremor	253	3.90	Labeled
14	Vomiting	237	3.65	Labeled
15	Diarrhoea	220	3.39	Labeled
16	Alanine Aminotransferase Increased	209	3.22	Labeled
17	Agitation	203	3.13	Labeled
18	Suicidal Ideation	200	3.08	Labeled
19	Aspartate Aminotransferase Increased	180	2.77	Labeled
20	***Fall***	***180***	***2.77***	***Not Labeled***
21	Asthenia	175	2.70	Labeled
22	Hepatic Enzyme Increased	167	2.57	Labeled
23	Loss of Consciousness	166	2.56	Labeled
24	Convulsion	160	2.47	Labeled
25	Malaise	158	2.43	Labeled
26	Constipation	155	2.39	Labeled
27	Paraesthesia	154	2.37	Labeled
28	Hypertension	152	2.34	Labeled
29	Confusional State	149	2.30	Labeled
30	Pain	147	2.27	Labeled
31	Drug Interaction*	140	2.16	-------
32	Dry Mouth	138	2.13	Labeled
33	Drug Withdrawal Syndrome	129	1.99	Labeled
34	***Dyspnoea***	***123***	***1.90***	***Not Labeled***
35	**Crying**	**120**	**1.85**	**Labeled for infants**
36	Weight Increased	118	1.82	Labeled
37	Irritability	117	1.80	Labeled
38	Vision Blurred	116	1.79	Labeled
39	Heart Rate Increased	115	1.77	Labeled
40	Prescribed Overdose	115	1.77	----------
41	Suicide Attempt	112	1.73	Labeled
42	Anorexia	108	1.66	Labeled
43	***Chest Pain***	***108***	***1.66***	***Not Labeled***
44	Nervousness	104	1.60	Labeled
45	Hallucination	99	1.53	Labeled
46	Abdominal Pain Upper	95	1.46	Labeled
47	Completed Suicide	86	1.33	Labeled
48	Condition Aggravated	86	1.33	Labeled
49	Pruritis	85	1.31	Labeled
50	Weight Decreased	85	1.31	Labeled

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21427	ORIG-1	ELI LILLY AND CO	CYMBALTA(DULOXETINE HCL)20,30,40,6OMG
NDA-21733	ORIG-1	ELI LILLY AND CO	CYMBALTA (DULOXETINE HYDROCHLORIDE)20/30
NDA-22148	ORIG-1	ELI LILLY AND CO	CYMBALTA
NDA-22516	ORIG-1	ELI LILLY AND CO	CYMBALTA

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/s/

LAURELLE CASCIO
07/19/2010

IDA-LINA DIAK
07/19/2010

MARK I AVIGAN
07/19/2010

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	July 12, 2010
To:	Ellen Fields, MD Medical Officer Division of Anesthesia, and Analgesia Products (DAAP) Office of New Drugs
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Subject:	Cymbalta® (duloxetine HCl) Drug Utilization Review
Drug Name(s):	Cymbalta® (duloxetine HCl)
Application Type/Number:	NDA 22-516
Applicant/sponsor:	Eli Lilly and Company
OSE RCM #:	2010-1208

EXECUTIVE SUMMARY

Division of Anesthesia and Analgesia Products (DAAP) requested drug utilization data for Cymbalta® (duloxetine HCl) in support of the Anesthetic and Life Support Drugs Advisory Committee to be held on August 19, 2010. The focus of this meeting is to discuss the risk and benefits of approving Cymbalta® (duloxetine HCl) for treatment of chronic pain. This analysis provides the utilization trends for Cymbalta® (duloxetine HCl) from drug approval in August 2004 through year 2009.

- Total dispensed prescriptions of Cymbalta® (duloxetine HCl) increased from approximately 5 million prescriptions in year 2005 to approximately 14.6 million prescriptions in year 2009 accounting for approximately 3-fold increase
- Cymbalta® (duloxetine HCl) 60 mg was the most commonly dispensed strength accounting for approximately 65% of total Cymbalta® (duloxetine HCl) dispensed prescriptions
- Approximately 80% of total dispensed Cymbalta® (duloxetine HCl) prescriptions were in patient age group 25-64 years old
- Approximately three-quarters of total dispensed prescriptions of Cymbalta® (duloxetine HCl) were dispensed to female patients
- Total number of unique patients receiving prescription of Cymbalta® (duloxetine HCl) in outpatient retail pharmacies increased from approximately 1.4 million patients in year 2005 to 2.8 million patients in year 2009 accounting for approximately 2 fold increase
- "General Practice/Family Medicine/Doctor of Osteopathy" was the top prescribing specialty group for Cymbalta® (duloxetine HCl) followed by "Psychiatry" and "Internal Medicine"
- Approximately one third of the diagnosis codes recorded that were associated with Cymbalta® (duloxetine HCl) use were for labeled indications such as "Major Depressive Disorder"(ICD-9 296.2 and 296.3), "Generalized Anxiety Disorder" (ICD-9 300-.2), "Fibromyalgia" (ICD-9 729.1) and "Diabetic Peripheral Neuropathy" (ICD-9 250.6 and 357.2)
- "Depressive Disorder, not elsewhere specified" (ICD-9 311.0) was the most common diagnosis code recorded (29.2%) that was associated with Cymbalta® (duloxetine HCl) use
- Approximately 7% of the diagnosis codes recorded were associated with "diseases of musculoskeletal system and connective tissue" (ICD-9 codes 710-739) which include chronic pain conditions such as arthritis and back pain
- Approximately 6.5% of the diagnosis codes recorded were associated with "headaches and nerve pain" (ICD-9 codes 337-359) which include "Chronic Pain Syndrome" (ICD-9 338.4) and "Chronic Pain, NOS" (ICD-9 338.2)

1 INTRODUCTION

The Division of Anesthesia and Analgesia Products is conducting an Advisory Committee Meeting on August 19, 2010 to discuss the risks and benefits of approving Cymbalta® (duloxetine HCl) for indication of chronic pain treatment, NDA 22-516. In support of the review of this new drug application, the Division of Epidemiology has been requested to provide drug utilization patterns of Cymbalta®

(duloxetine HCl). Using the currently available proprietary drug use databases licensed by the Agency, this review provides overall sales data, use by indication, and prescriber specialty from drug approval in August 2004 through year 2009.

2 BACKGROUND

Cymbalta® (duloxetine HCl) is a serotonin and norepinephrine reuptake inhibitor (SNRI) and is indicated for Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), Diabetic Pheripheral Neuropathy (DPN), and Fibromyalgia (FM) in adults.[1] The Agency is currently reviewing a new drug application (NDA), 22-516 for Cymbalta® (duloxetine HCl) for treatment of chronic pain. On August 19, 2010 an advisory committee meeting will be convened before the members of the Anesthetic and Life Support Drug Committee and will discuss the available safety and efficacy data for Cymbalta® (duloxetine HCl) as they relate to the proposed indication of treatment of chronic pain. To understand the utilization patterns, assess labeled and off labeled indications, and assess number of prescriptions stratified by prescriber specialty for Cymbalta® (duloxetine HCl), this drug utilization review provides the outpatient trends from drug approval in August 2004 through year 2009.

3 METHODS AND MATERIAL

3.1 DETERMINING SETTINGS OF CARE

IMS Health, IMS National Sales Perspectives™ data (***see Appendix 2 for detailed database descriptions***) were used to determine the setting in which Cymbalta® (duloxetine HCl) was sold. Sales of Cymbalta® (duloxetine HCl) by number of individual packages (Eaches) sold from the manufacturer into the various retail and non-retail channels of distribution were analyzed for the year of 2009 ***(data not provided)***. Retail pharmacy settings (chain stores, independent pharmacies, and food stores) accounted for approximately 76% of Cymbalta® sales.[2] Since the majority of the Cymbalta® (duloxetine HCl) market share was sold to U.S. outpatient retail settings, this review focused on the outpatient retail pharmacy utilizations, excluding mail order channels.

3.2 DATA SOURCES

Proprietary drug use databases licensed by the Agency were used to conduct this analysis. Outpatient drug utilization was measured from SDI, Vector One®: National (VONA). From these data sources, the estimates of the total annual number of prescriptions dispensed were obtained for Cymbalta® (duloxetine HCl) from year 2004 through year 2009. We also obtained the number of dispensed prescriptions stratified by the prescribing specialties for an aggregate time period from approval in August 2004 through April 2010. In addition, the number of patients receiving a dispensed prescription for Cymbalta® (duloxetine HCl) in the outpatient setting was obtained from the SDI, Total Patient Tracker database for year 2004 through year 2009. Diagnoses associated with the use of Cymbalta® (duloxetine HCl) were obtained from the SDI, Physician Drug and Diagnosis Audit ™ for an aggregate time period from August 2004 through April 2010 (***see Appendix 2 for detailed database descriptions***).

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[1] Cymbalta® (duloxetine) label-http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/022148lbl.pdf

[2] IMS Health, IMS Nationals Sales Perspectives™, Data extracted 6/10. Source File: 1006cymb.DVR

4 RESULTS

4.1 OUTPATIENT DISPENSED PRESCRIPTIONS FOR CYMBALTA® (DULOXETINE)

Table 1 in ***Appendix 1*** displays the total number of projected dispensed prescriptions of Cymbalta® (duloxetine HCl) in outpatient retail pharmacies for years 2004 to 2009. Cymbalta® (duloxetine HCl) prescriptions increased from approximately 5 million prescriptions in year 2005 to approximately 14.6 million prescriptions in year 2009 in U.S. outpatient retail pharmacies. Cymbalta® (duloxetine) 60mg was the most commonly dispensed strength followed by 30mg and 20mg in year 2004 through year 2009.

4.2 OUTPATIENT DISPENSED PRESCRIPTIONS FOR CYMBALTA® (DULOXETINE) STRATIFIED BY AGE

Table 2 in ***Appendix 1*** displays the total number of projected dispensed prescriptions of Cymbalta® (duloxetine HCl) by age (0-17, 18-24, 25-64, 65+ years) in U.S. outpatient retail pharmacies in year 2004 through year 2009.

The data stratified by age indicate that approximately 78% of total Cymbalta® (duloxetine HCl) prescriptions were dispensed to patient age group 25-64 years of age in year 2009. Although total number of prescriptions increased from 3.9 million to 11.4 million (approximately 3 fold increase) from year 2005 through year 2009, the percent share of total Cymbalta® (duloxetine HCl) prescriptions for patient age group (25-64 years of age) relatively remained consistent.

Total number of Cymbalta® (duloxetine HCl) prescriptions in age group 0-17 years and 18-24 years of age increased but the percent share gradually decreased in both age groups. In patient age group 0-17 years of age, the total number of Cymbalta® (duloxetine HCl) prescriptions increased from approximately 53 thousand in year 2005 to approximately 94 thousand in year 2009 but the percent share of total Cymbalta® (duloxetine HCl) prescriptions for patient age group 0-17 years of age gradually decreased from 1.1% in year 2005 to 0.6% in year 2009.

Similarly, in patient age group 18-24 years of age the total number of Cymbalta® (duloxetine HCl) prescriptions increased from approximately 162 thousand in year 2005 to approximately 345 thousand prescriptions in year 2009, but the percent share of total Cymbalta® (duloxetine HCl) prescriptions for patient age group 18-24 years old gradually decreased from 3.3% in year 2005 to 2.4% in year 2009.

In contrast, in patient age group 65 years of age and above, total number of Cymbalta® (duloxetine HCl) prescriptions increased from approximately 758 thousand prescriptions in year 2005 to approximately 2.8 million prescriptions in year 2009 (approximately 3.5 fold increase); the percent share also increased from 13% in year 2005 to 19% in year 2009. In all age groups, Cymbalta® (duloxetine HCl) 60mg strength was the most commonly dispensed throughout the study period of year 2004 through year 2009 (table 3 in ***Appendix 1***).

4.3 OUTPATIENT DISPENSED PRESCRIPTIONS FOR CYMBALTA® (DULOXETINE) STRATIFIED BY SEX

Table 4 in ***Appendix 1*** displays the total number of projected dispensed prescriptions of Cymbalta® (duloxetine HCl) by patient sex and drug strength in U.S. outpatient pharmacies in year 2004 through year 2009. Female patients accounted for approximately three-quarters and male patients accounted for approximately one-quarter of total Cymbalta® (duloxetine HCl) prescriptions in year 2004 through year 2009. Total number of Cymbalta® (duloxetine HCl) prescriptions in females increased from approximately 3.5 million prescriptions in year 2005 to approximately 10.8 million (3 fold increase) in year 2009. Similarly, total number of Cymbalta® (duloxetine HCl) prescriptions in males increased from approximately 1.3 million prescriptions in year 2005 to approximately 3.8 million (3 fold increase)

in year 2009. In females and males, the most common strength of Cymbalta® (duloxetine HCl) dispensed was 60mg followed by 30mg and 20 mg in year 2004 through year 2009.

4.4 NUMBER OF PATIENTS RECEIVING PRESCRIPTIONS FOR CYMBALTA® (DULOXETINE HCL)

Table 5 in ***Appendix 1*** displays the total number of projected unique patients receiving a dispensed prescription of Cymbalta® (duloxetine HCl) from outpatient retail pharmacies in year 2004 through 2009. Trends for patient data were similar to prescription data. Approximately 1.4 million unique patients received a prescription for Cymbalta® (duloxetine HCl) in year 2005. The number of unique patients increased to 2.8 million patients in year 2009 (increased by 2 fold from year 2005).

4.5 DISPENSED PRESCRIPTIONS BY PRESCRIBER SPECIALTY

Figure 1 in ***Appendix 1*** shows the number of dispensed prescriptions of Cymbalta® (duloxetine HCl) by top prescribing specialties for an aggregate time period from approval in August 2004 through April 2010. "General Practice/Family Medicine/Osteopathy" (28%) group was the top prescribing specialty for Cymbalta® (duloxetine HCl), followed by "Psychiatry" (24%), "Internal Medicine" (17%) and "Nurse Practitioners" (6%).

"Neurologist" (4%), "Physician Assistants" (2%), "Anesthesiologist" (2%), "Rheumatologists" (2%), and "Physical Medicine and Rehabilitation Specialist" (2%) were also in the top 10 groups of prescribers.

4.6 DIAGNOSES ASSOCIATED WITH THE USE OF CYMBALTA® (DULOXETINE)

Table 6 in ***Appendix 1*** displays the diagnosis (ICD-9) associated with the use of Cymbalta® (duloxetine HCl) for an aggregate time period from approval time in August 2004 through April 2010. According to the office-based physician practices in the U.S., approximately one-third (33%) of the diagnosis codes recorded that were associated with Cymbalta® (duloxetine HCl) use were for labeled indications such as "Major depressive disorder, single episode" (ICD-9 296.2), "Major depressive disorder, recurrent episode"(ICD-9 296.3), "Generalized Anxiety Disorder" (ICD-9 300.02), "Fibromyalgia" (ICD-9 729.1) and "Diabetic Peripheral Neuropathy" (ICD-9 250.6 and 357.2). Approximately two-thirds (67%) of the diagnosis codes recorded that were associated with Cymbalta® (duloxetine HCl) use were for off-labeled indications. Of all the diagnoses, "Depressive Disorder, not elsewhere specified" (ICD-9 311.0) was the most common diagnosis code recorded that was associated with Cymbalta® (duloxetine HCl) use (29.5%). Approximately 7.3% of the diagnosis codes were associated with "diseases of musculoskeletal system and connective tissue" (ICD-9 codes 710-739) which includes chronic pain conditions such as arthritis and back pain, and approximately 6.5% of the diagnosis codes were associated with "headaches and nerve pain" (ICD-9 codes 337-359) which includes "Chronic Pain Syndrome" (ICD-9 338.4) and "Chronic Pain, NOS" (ICD-9 338.2).

5 DISCUSSION

Based on these findings, patients with "diseases of musculoskeletal system and connective tissue" (ICD-9 codes 710-739) (7.3% of total diagnosis codes) could translate into approximately 200 thousand patients for year 2009 and a total of approximately 1 million prescriptions of Cymbalta® (duloxetine HCl) for year 2009. Adding in patients with "headaches and nerve pain" (ICD-9 codes 337-359) (6.5% of total diagnosis codes), an additional 200 thousand patients and 1 million prescriptions may be exposed for these off-labeled pain conditions.

The greatest proportion of prescribing are from General Practice/Family Medicine/Osteopathy physicians; however, specialists such as anesthesiologists and rheumatologists were among the top 10 prescribers of Cymbalta® (duloxetine HCl), albeit in lower proportions. Hence, the approval of a chronic pain indication may increase prescribing levels from these specialists.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that Cymbalta® (duloxetine HCl) is distributed primarily to the retail outpatient setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these outpatient retail pharmacy channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

This review analyzed data from the outpatient retail pharmacy setting only, which accounts for approximately 76% of the total distribution volume of the selected sales market. Up to 24% of the total distribution volume going into mail order and non-retail settings was not analyzed.

SDI uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Indications for use were obtained using SDI's PDDA, a monthly survey of 3,200 office based physicians. Although PDDA data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, PDDA data are best used to identify the typical uses for the products in clinical practice, and the VONA outpatient prescription data to evaluate trends over time.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

6 CONCLUSIONS

Using the strictest definitions for labeled indications, we estimate that nearly two-thirds of use for Cymbalta® (duloxetine HCl) may be used off-label and that nearly 14% of drug use may be used for off-labeled pain conditions such as "diseases of musculoskeletal system and connective tissue" (7.3%) and "headaches and nerve pain" (6.5%). Approving the use of Cymbalta® (duloxetine HCl) for chronic pain may increase the patient exposure and physician prescribing to an area that is already not uncommon.

APPENDIX 1: Tables and Figures

TABLE 1

Total number of prescriptions for Cymbalta® (duloxetine) by strength dispensed in U.S. outpatient retail pharmacies, 2004-2009

	2004		2005		2006		2007		2008		2009	
	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%
duloxetine hcl	558,214	100.0%	4,938,368	100.0%	8,520,352	100.0%	12,550,576	100.0%	14,421,962	100.0%	14,653,155	100.0%
60MG	352,744	63.2%	3,223,246	65.3%	5,558,893	65.2%	8,228,121	65.6%	9,582,886	66.4%	9,844,284	67.2%
30MG	162,670	29.1%	1,366,057	27.7%	2,409,118	28.3%	3,570,072	28.4%	4,095,101	28.4%	4,141,517	28.3%
20MG	42,800	7.7%	349,065	7.1%	552,341	6.5%	752,383	6.0%	743,975	5.2%	667,354	4.6%

Source: SDI: Vector One® National, data extracted 06-2010, Source: VONA 2010-1208 Duloxetine Strength 6-23-10(1).xls

TABLE 2

Total number of prescriptions for Cymbalta® (duloxetine) by age dispensed in U.S. outpatient retail pharmacies, 2004-2009

	2004		2005		2006		2007		2008		2009	
	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%
duloxetine hcl	558,193	100.0%	4,938,356	100.0%	8,520,338	100.0%	12,550,542	100.0%	14,421,940	100.0%	14,653,155	100.0%
0-17	7,759	1.4%	53,169	1.1%	71,298	0.8%	91,878	0.7%	94,588	0.7%	93,985	0.6%
18-24	22,117	4.0%	161,709	3.3%	239,640	2.8%	336,000	2.7%	372,125	2.6%	345,567	2.4%
25-64	447,741	80.2%	3,901,798	79.0%	6,785,356	79.6%	9,984,362	79.6%	11,392,930	79.0%	11,393,821	77.8%
65+	73,404	13.2%	757,771	15.3%	1,383,165	16 2%	2,097,603	16.7%	2,525,154	17.5%	2,785,368	19.0%
UNSPEC	7,172	1.3%	63,909	1.3%	40,879	0.5%	40,699	0.3%	37,143	0.3%	34,413	0 2%

Source: SDI: Vector One® National, data extracted 07-2010, Source: VONA 2010-1208 _Duloxetine_age_07-02-10(1) xls

TABLE 3

Total Number of Prescriptions for Cymbalta® (Duloxetine) by age and strength dispensed in U.S. Outpatient Retail Pharmacies, 2004-2009

	2004		2005		2006		2007		2008		2009	
	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%
duloxetine hcl	558,193	100.0%	4,938,356	100.0%	8,520,338	100 0%	12,550,542	100.0%	14,421,940	100.0%	14,653,155	100.0%
0-17	7,759	1.4%	53,169	1.1%	71,298	0 8%	91,878	0.7%	94,588	0.7%	93,985	0.6%
60MG	3,910	50.4%	27,990	52.6%	35,644	50 0%	44,696	48.6%	46,558	49.2%	45,460	48.4%
30MG	3,178	41.0%	18,904	35.6%	25,963	36.4%	33,915	36.9%	34,210	36.2%	34,296	36.5%
20MG	671	8.6%	6,275	11 8%	9,691	13.6%	13,267	14.4%	13,820	14.6%	14,230	15.1%
18-24	22,117	4.0%	161,709	3 3%	239,640	2 8%	336,000	2.7%	372,125	2.6%	345,567	2.4%
60MG	14,043	63.5%	103,484	64 0%	147,019	61 3%	203,791	60.7%	226,192	60.8%	213,312	61.7%
30MG	6,595	29.8%	45,787	28 3%	72,632	30 3%	104,242	31.0%	117,056	31.5%	109,162	31.6%
20MG	1,479	6.7%	12,438	7.7%	19,989	8 3%	27,967	8.3%	28,877	7.8%	23,094	6.7%
25-64	447,741	80.2%	3,901,798	79 0%	6,785,356	79.6%	9,984,362	79.6%	11,392,930	79.0%	11,393,821	77.8%
60MG	290,825	65.0%	2,620,591	67 2%	4,544,849	67 0%	6,719,519	67.3%	7,764,883	68.2%	7,855,110	68.9%
30MG	124,818	27.9%	1,025,811	26 3%	1,831,760	27 0%	2,711,531	27.2%	3,092,338	27.1%	3,070,308	26.9%
20MG	32,098	7.2%	255,396	6 5%	408,747	6 0%	553,312	5.5%	535,709	4.7%	468,404	4.1%
65+	73,404	13.2%	757,771	15 3%	1,383,165	16 2%	2,097,603	16.7%	2,525,154	17.5%	2,785,368	19.0%
60MG	39,841	54.3%	430,907	56 9%	805,432	58 2%	1,233,119	58.8%	1,519,722	60.2%	1,706,889	61.3%
30MG	25,459	34.7%	255,461	33.7%	466,011	33.7%	708,823	33.8%	841,325	33.3%	917,966	33.0%
20MG	8,104	11.0%	71,403	9.4%	111,722	8.1%	155,661	7.4%	164,107	6.5%	160,513	5.8%
UNSPEC	7,172	1.3%	63,909	1 3%	40,879	0 5%	40,699	0.3%	37,143	0.3%	34,413	0.2%

Source: SDI, Vector One ® National: Years 2004-2009, Extracted July 2010 File Name: VONA 2010-1208 Duloxetine age strength07-06-10(1).xls

TABLE 4

Total number of prescriptions for Cymbalta® (duloxetine) by gender and strength dispensed in U.S. outpatient retail pharmacies, 2004-2009

	2004		2005		2006		2007		2008		2009	
	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%	TRxs	Share%
duloxetine hcl	558,193	100.0%	4,938,356	100.0%	8,520,338	100.0%	12,550,542	100 0%	14,421,940	100 0%	14,653,155	100.0%
Female	399,235	71.5%	3,543,509	71.8%	6,255,842	73.4%	9,237,412	73.6%	10,611,428	73.6%	10,808,676	73.8%
60MG	251,798	63.1%	2,305,457	65.1%	4,056,619	64.8%	6,020,456	65 2%	7,008,177	66 0%	7,224,304	66.8%
30MG	116,554	29.2%	984,487	27.8%	1,786,265	28.6%	2,651,702	28.7%	3,042,666	28.7%	3,083,117	28.5%
20MG	30,883	7.7%	253,565	7.2%	412,958	6.6%	565,254	6.1%	560,585	5 3%	501,254	4.6%
Male	150,550	27.0%	1,311,602	26.6%	2,222,472	26.1%	3,268,272	26 0%	3,762,639	26.1%	3,793,474	25.9%
60MG	96,012	63.8%	864,373	65.9%	1,475,270	66.4%	2,178,255	66.6%	2,542,543	67.6%	2,585,599	68.2%
30MG	43,072	28.6%	356,796	27.2%	610,465	27.5%	905,397	27.7%	1,038,478	27.6%	1,043,723	27.5%
20MG	11,466	7.6%	90,433	6.9%	136,737	6.2%	184,620	5.6%	181,618	4 8%	164,152	4.3%
UNSPEC	8,408	1.5%	83,245	1.7%	42,024	0.5%	44,858	0.4%	47,873	0 3%	51,005	0.3%

Source: SDI: Vector One® National, data extracted 07-2010, Source: VONA 2010-1208 _Duloxetine_gender_strength_07-02-10(1).xls

TABLE 5

Total number of unique patients receiving a dispensed prescription for Cymbalta ® (duloxetine) from U.S. outpatient retail pharmacies, Years 2004-2009

	Years					
	2004	2005	2006	2007	2008	2009
Unique Patients*	318,651	1,408,766	2,103,719	2,729,110	2,966,302	2,828,372

*Do not add across years, summing across years will result in double counting and overestimates of patient counts. *SDI, Total Patient Tracker, Year 2004-2010, Extracted June 2010*

FIGURE 1

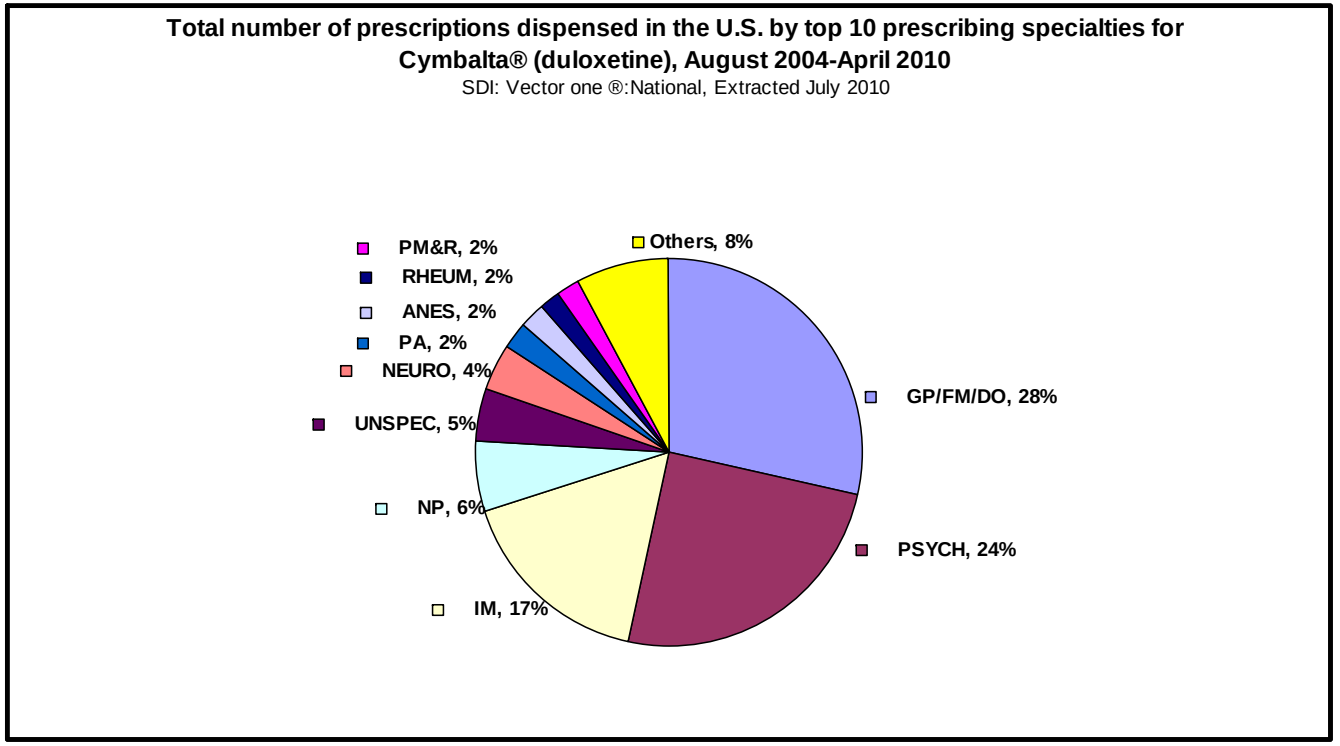

TABLE 6

Diagnosis associated with use (by grouped ICD-9 codes) for Cymbalta® (duloxetine HCl) as reported by office-based physicians in the U.S., August 2004-April 2010

	August 2004- April 2010		
		Uses (000)	Share %
Total Cymbalta Market		**30,902**	*100.0%*
Labeled Indications	**ICD-9**		*33%*
Diabetic Peripheral Neuropathy (DPN)	**357.2 and 250.6**	**1,524**	*4.9%*
Major Depressive Disorder (MDD)	**296.2 and 296.3**	**6,321**	*20.5%*
Generalized Anxiety Disorder (GAD)	**300.02**	**589**	*1.9%*
Fibromyalgia (FM)	**729.1**	**1,845**	*6.0%*
Unlabeled Indications			*67%*
Other Psych Disorders (excluding MDD and GAD)		**15272**	*49.4%*
Neoplasms (140-239)		**24**	*0.1%*
Headaches and Nerve Pain (337-359, excluding 357.2)		**1996**	*6.5%*
Diseases of the musculoskeletal system & connective tissue (710-739, excluding 729.1)		**2258**	*7.3%*
Fever & General Symptoms (780-789)		**394**	*1.3%*
Fractures, Sprains, Contusions, Injuries (800-999)		**96**	*0.3%*
All Others		**624**	*2.0%*

Source: SDI, Physicians Drug and Diagnosis Audit, 08/04-04/09, Extracted 6/10, File: PDDA 2010-1208 Cymbalta Dx6 07-7-10.xls

APPENDIX 2: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

SDI Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI Vector One®: Total Patient Tracker (TPT)

SDI's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

SDI Physician Drug & Diagnosis Audit (PDDA) with Pain Panel

SDI's Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22516	ORIG-1	ELI LILLY AND CO	CYMBALTA

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/s/

RAJDEEP K GILL
07/13/2010

LAURA A GOVERNALE
07/13/2010
Cleared for background package.

REVIEW AND EVALUATION OF PROPOSED LABEL FOR DULOXETINE

NDA: 21427 (GAD & MDD) , 22516 (Chronic Pain)
SPONSOR: Eli Lilly and Company
DRUG: Duloxetine (Cymbalta ^{TM})
DRUG CATEGORY: SSNRI (Selective Serotonin/Norepinepherine Reuptake Inhibitor)
MATERIAL SUBMITTED: Proposed label revisions from DAAP for new indication of chronic pain: NDA 22516.

I. Background

The Division of Anesthesia and Analgesia Products asked DPP to evaluate the proposed changes in the sponsor's submitted labeling (for the indication of chronic pain) as it relates to MDD and GAD. It appears that the sponsor has changed the exposure numbers for the placebo controlled data for both MDD and GAD from the last agreed on labeling (see Approval letter 11/19/2009 for NDA 21427 for GAD).

II. Label Comparison

A. Proposed labeling changes in NDA 22516 for Section 6.1(changes are highlighted)

(b) (4)

B. Approved label for Section 6.1 (as per approval letter for GAD: 11/19/2009)

"…The data described below reflect exposure to duloxetine in placebo-controlled trials for MDD (N=2,327), GAD (N=668), DPNP (N=568), and FM (N=876). The population studied was 17 to 89 years of age; 64.8%, 64.7%, 38.7%, and 94.6% female; and 85.5%, 84.6%, 77.6%, and 88% Caucasian for MDD, GAD, DPNP, and FM, respectively…"

III. Conclusion

It is unclear what new data the sponsor is utilizing to support their increased exposure numbers for both the indications of GAD and MDD in their newly proposed labeling. The increased "N" for GAD and MDD are not consistent with the most recently approved label (see Action letter dated 11/19/2009 for GAD approval: NDA 21-427). It is also noted that, in the sponsor's new proposed labeling, the sponsor did not revise the exposure numbers (for the denominator) in Section 6.2 when calculating the incidence of adverse events in the GAD (n=668) and MDD (b) (4) placebo controlled trials (Section 6.2 is consistent with the approved label of 11/19/2009).

IV, Recommendation

It is recommended that the sponsor clarify and provide data to support their proposed changes to the exposure numbers for the placebo-controlled data for MDD and GAD. These new numbers are inconsistent with the approved label of 11/19/2009 and inconsistent with the denominators used to calculate the incidence of adverse events in Section 6.2 of the proposed and approved label.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22516	ORIG-1	ELI LILLY AND CO	CYMBALTA

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/s/

ROBERTA L GLASS
05/06/2010

JING ZHANG
05/07/2010

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: February 24, 2010

To: Ayanna Augustus – Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

From: Mathilda Fienkeng – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: **DDMAC draft labeling comments**
NDA 22-516 Cymbalta (duloxetine hydrochloride) Delayed-Release Capsules for Oral Use

DDMAC has reviewed the proposed product labeling (PI), and container labeling for Cymbalta (duloxetine hydrochloride) Delayed-Release Capsules for Oral Use, submitted for consult on November 25, 2009.

The following comments are provided using the updated proposed PI sent via email on February 05, 2010 by Ayanna Augustus. DDMAC has reviewed the proposed container labeling and has no comments. If you have any questions about DDMAC's comments, please do not hesitate to contact us.

31 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22516	ORIG-1	ELI LILLY AND CO	CYMBALTA

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/s/

MATHILDA K FIENKENG
02/24/2010

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: February 12, 2010

TO: Ayanna Augustus, Regulatory Project Manager
Anjelina Pokrovnichka, M.D., Medical Officer
Division of Anesthesia, Analgesia and Rheumatology Products

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: #22-516

APPLICANT: Eli Lilly & Company

DRUG: Cymbalta (duloxetine)

NME: No

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Treatment of chronic pain (CP) including pain of osteoarthritis and lower back pain

CONSULTATION REQUEST DATE: October 8, 2009

DIVISION ACTION GOAL DATE: March 15, 2010
PDUFA DATE: March 15, 2010

I. BACKGROUND:

Eli Lilly and Company has submitted NDA 22-516 for duloxetine for the indication of chronic pain (CP) including treatment of chronic pain of osteoarthritis and chronic lower back pain. Clinical inspections were conducted in response to a routine audit request to assess data integrity and human subject protection for clinical trials conducted for approval. The efficacy results of three studies are important in making a regulatory decision with regard to drug approval. Selection of sites was based on numbers of subjects enrolled at the site. In addition, Dr. Bart's site demonstrated efficacy results that were more unbalanced between treatment and placebo groups than the other centers in Study HMFG.

The protocols inspected included:

A. Protocol F1J-MC-HMEN entitled "Effect of Duloxetine 60 mg to 120 mg Once Daily in Patients with Chronic Low Back Pain"

B. Protocol F1J-MC-HMFG entitled "Duloxetine 60 to 120 mg versus Placebo in the Treatment of Patients with Osteoarthritis Knee Pain"

C. Protocol F1J-MC-HMGC entitled "Effect of Duloxetine 60 mg Once Daily versus Placebo in Patients with Chronic Low Back Pain."

II. RESULTS (by Site):

Name of Clinical Investigator (CI) and Location	Protocol # / # of Subjects	Inspection Date	Final Classification
CI #1 Dr. Henk Mulder Rotterdam Research Institute Eudractnr. 2006-003484-31 Schieweg 52a Rotterdam 3039 BD, Netherlands	F1J-MC-HMEN/ Site # 301/ 41 subjects randomized	August 31 to September 4, 2009	NAI
CI #2 Dr. Yuri Belenkov Moscow Medical Academy 6, Building 1 Pirogovskaya Str. Moscow, 119992, Russia	F1J-MC-HMEG/ Site #032/ 39 subjects randomized	November 16 to 20, 2009	VAI
CI#3 Dr. Boris Bart Russian State Medical University 29, Building 2 Miklukho-Maklaya Str. Moscow, 117485, Russia	F1J-MC-HMEG/ Site #034/ 15 subjects randomized	November 23 to 27, 2009	VAI
CI#4 Bruce Rankin, D.O. Avail Clinical Research LLC 860 Peachwood Dr. Deland, FL 32720	F1J-MC-HMGC/ Site #75/ 34 subjects randomized	January 4 to 12, 2010	Pending (Preliminary classification VAI)
CI#5 Kyle Patrick, D.O. Radiant Research of Phoenix 924 W. Chandler Blvd Chandler, AZ 85225	F1J-MC-HMGC/ Site #74/ 26 subjects randomized	November 19 to December 9, 2009	VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.

1. Dr. Henk Mulder
Rotterdam Research Institute
Eudractnr. 2006-003484-31, Schieweg 52a
Rotterdam 3039 BD, Netherlands

a. **What was inspected**: For Protocol F1J-MC-HMEN at this site, 64 subjects were screened, and there were 23 screen failures. Forty-one (41) subjects were randomized. Including the "extension phase" of the study, 8 subjects discontinued from the "acute phase" of the study, and an additional 10 subjects discontinued during the "extension phase." For both phases, a total of 23 subjects completed the study. An audit was conducted of informed consent documents for all subjects screened for the trial. A detailed audit of 7 of 41 randomized subjects' records (17%) was conducted, including, but not limited to, handwritten progress notes, study-specific source documents and questionnaires, eligibility criteria, (b) (4) laboratory requisition forms and laboratory reports, radiology reports, ECG printouts, data queries, and protocol deviations.

b. **General observations/commentary:** Primary efficacy endpoint data for 34 of 41 randomized study subjects (83%) were reviewed and verified. There was no under reporting of adverse events. In a single instance, the source document did not agree with the line listing in the NDA. For Subject 3112, Visit 5 average BPI is listed as "3" in the NDA line listings. In the source document, the value was originally recorded as "3" but then changed to a "2." This change is noted with an illegible date and/or initial. No Form FDA-483 was issued as no significant issues were identified.

c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. Dr. Yuri Belenkov
Moscow Medical Academy, 6, Building 1 Pirogovskaya Str.
Moscow, 119992, Russia

a. **What was inspected:** For Protocol F1J-MC-HMEG 40 subjects were screened and 39 subjects were randomized and completed the study. An audit of all subjects' records was conducted.

b. **General observations/commentary:** There was no under-reporting of adverse events. A Form FDA-483 was issued to the CI after inspection revealed that the clinical investigator did not conduct the investigation in accordance with the investigational plan. The sponsor submitted data to the NDA concerning this deviation in Section 10.2 "Protocol Violations" of the F1J-MC-HMFG clinical study report. Specifically, the following 12 subjects: Subjects 3201, 3204, 3205, 3206, 3207, 3209, 3210, 3211, 3212, 3214, 3217, and 3218, received medication from only one bottle instead of two bottles

for the interval between Visits 4 and 5. Dr. Belenkov adequately responded to the inspectional findings in a letter dated December 3, 2009. The deficiencies above were discovered by the sponsor during monitoring and were reported by the sponsor to the FDA. They appear to have been the result of unclear instructions in the protocol and were not a result of systematic violations in the conduct of the trial.

c. **Assessment of data integrity**: The protocol violations noted above were reported in the clinical study report, and decision concerning use of the data for the subjects listed above is deferred to the review division. Except for these violations, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

3. Dr. Boris Bart
Russian State Medical University, 29, Building 2
Miklukho-Maklaya Str., Moscow, 117485, Russia

a. **What was inspected**: For Protocol F1J-MC-HMEG at this site, 16 subjects were screened, and 15 subjects were randomized and completed the study. An audit of all randomized subjects' records was conducted.

b. **General observations/commentary**: A form FDA-483 was issued after the inspection revealed that the clinical investigator did not conduct the investigation in accordance with the investigational plan. The sponsor submitted data to the NDA concerning this deviation in F1J-MC-HMFG clinical study report Section 10.2 "Protocol Violations." Specifically, Subjects 3401, 3403, and 3206, received medication from only one bottle instead of two bottles for the interval between Visits 4 and 5. The deficiencies above were discovered by the sponsor during monitoring and were reported by the sponsor to the FDA. They appear to have been the result of unclear instructions in the protocol and were not a result of systematic violations in the conduct of the trial.

c. **Assessment of data integrity**: The protocol violations noted above were reported in the clinical study report, and decision concerning use of the data for the subjects listed above is deferred to the review division. Except for these violations, the study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

4. Bruce Rankin, D.O.
Avail Clinical Research LLC
860 Peachwood Dr., Deland, FL 32720

Note: Observations noted for this site are based on communications with the FDA investigator and review of the FDA Form 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection

Report (EIR). Preparation of the EIR has been delayed because copies of documents related to the inspection of the Rankin site for NDA 22-516 were stolen from the FDA investigator. Dr. Rankin has been notified.

a. **What was inspected:** For Protocol F1J-MC-HMGC there were a total of 47 subjects screened, 34 subjects were enrolled, and 24 subjects completed the study. A total of 33 subjects' records were reviewed completely.

b. **General observations/commentary**: There was no evidence of under-reporting of adverse events, and the primary efficacy endpoint data were verified. A Form FDA 483 was issued because procedures for sample banking for pharmacogenetic studies specified in the "Protocol Sample Banking Addendum" were not followed. This did not impact data integrity.

c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

5. Kyle Patrick, D.O.
Radiant Research of Phoenix
924 W. Chandler Blvd, Chandler, AZ 85225

a. **What was inspected:** For Protocol F1J-MC-HMGC at this site, 38 subjects were screened, 26 subjects were randomized, and 20 subjects completed the study. Thirteen subjects' records were reviewed in their entirety. An audit of all subjects' consent forms and all primary efficacy endpoint records was conducted.

b. **General observations/commentary**: The primary endpoint data were verified. A Form FDA 483 was issued for failure to follow the protocol because the occurrence of drowsiness that occurred on April 17, 2009 and nausea that occurred on May 8, 2009, both in Subject 7437 (active) were not reported to the sponsor. All other AEs that occurred with this subject, including other episodes of nausea and hypersomnia were reported. These appear to be isolated instances of under-reporting of adverse events, and are unlikely to significantly impact study outcome.

c. **Assessment of data integrity**: The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Five clinical investigator sites were inspected in support of this application. The inspection of Dr. Henk Mulder did not find regulatory violations. The inspections of Drs. Belenkov, Bart, Rankin, and Patrick found violations as noted above. Violations note above for Drs.

Belenkov and Bart were reported in the clinical study report and decision concerning use of the data for these subjects is deferred to the review division. The data from all sites appear acceptable in support of the proposed indication.

Note: The final classification for the inspection of Dr. Rankin is pending. An addendum to this clinical inspection summary will be forwarded to the review division if additional observations of clinical and regulatory significance are discovered after reviewing the EIRs for Dr. Rankin.

{See appended electronic signature page}

Susan Leibenhaut, M. D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22516	ORIG-1	ELI LILLY AND CO	CYMBALTA

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/s/

SUSAN LEIBENHAUT
02/18/2010

TEJASHRI S PUROHIT-SHETH
02/18/2010

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 022516 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Cymbalta Established/Proper Name: duloxetine hydrochloride Dosage Form: capsules Strengths: 20, 30, and 60 mg		
Applicant: Eli Lilly and Company Agent for Applicant (if applicable):		
Date of Application: May 15, 2009 Date of Receipt: May 15, 2009 Date clock started after UN:		
PDUFA Goal Date: March 15, 2010	Action Goal Date (if different):	
Filing Date: July 14, 2009	Date of Filing Meeting: July 9, 2009	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 6		
Proposed indication(s)/Proposed change(s): chronic pain		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" form found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html*** ***and refer to Appendix A for further information.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☒ Standard ☐ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☒ Withdrawn NDA #: 22333	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical

Other:	benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (*if OTC product*):				
List referenced IND Number(s): (b) (4)				
Goal Dates/Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	**x**			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	**x**			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	**x**			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send UN letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☐ Not in arrears ☐ In arrears
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).*	

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?				
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).				
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))? ***Note:*** *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*				
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:				

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at:*** ***http://www.fda.gov/cder/ob/default.htm***		X		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 years ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance[1]? **If not,** explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	**X**			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	**X**			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? ***If yes,*** *date consult sent to the Controlled Substance Staff:*		**X**		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				

Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature? ***If foreign applicant, <u>both</u> the applicant and the U.S. agent must sign the form.***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information **(NDAs/NDA efficacy supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature? ***Forms must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***(Certification is not required for supplements if submitted in the original application)*** ***If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification.*** ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	X			

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	

Pediatrics	YES	NO	NA	Comment
PREA Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X			
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		
If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***	X			
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) ***If no, request in 74-day letter***	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***		X		

Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.***			X	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request PLR format in 74-day letter.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			
REMS consulted to OSE/DRISK?	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?		X		
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				

Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***				
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***		X		

Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** October 7, 2005 ***If yes, distribute minutes before filing meeting***	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** November 16, 2007 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** ***If yes, distribute letter and/or relevant minutes before filing meeting***		X		

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 9, 2009

BLA/NDA/Supp #: 22-516

PROPRIETARY NAME: Cymbalta

ESTABLISHED/PROPER NAME: duloxetine hydrochloride

DOSAGE FORM/STRENGTH: Capsule, 20, 30, and 60 mg

APPLICANT: Eli Lilly and Company

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): chronic pain

BACKGROUND: Lilly submitted an application for the management of chronic pain on May 15, 2008 (NDA 22-333), and subsequently withdrew this application on November 26, 2008 in order to add an additional data from a chronic pain in patients with osteoarthritis (OA) (study HMFG) and to better characterize the appropriate dose for patients with chronic pain. Cymbalta has been approved in the US for the treatment of major depressive disorder (MDD), and generalized anxiety disorder (GAD) under NDA 21-427, diabetic peripheral neuropathic pain (DPNP) under NDA 21-733 and fibromyalgia under NDA 22-148.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Ayanna Augustus	Y
	CPMS/TL:	Parinda Jani	N
Cross-Discipline Team Leader (CDTL)	Ellen Fields		Y
Clinical	Reviewer:	Anjelina Pokrovnichka	Y
	TL:	Ellen Fields	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		

Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Srikanth Nallani	Y
	TL:	Suresh Doddapaneni	N
Biostatistics	Reviewer:	Yongman Kim	Y
	TL:	Dionne Price	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Kathleen Yong	N
	TL:	Adam Wasserman	N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Danae Christodoulou	Y
	TL:		
Quality Microbiology *(for sterile products)*	Reviewer:		
	TL:		
CMC Labeling Review *(for BLAs/BLA supplements)*	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:	Sharon Mills	N
	TL:	Jody Duckhorn	N

Bioresearch Monitoring (DSI)	Reviewer:	Susan Leibenhaut	Y
	TL:		

Other reviewers		
Other attendees	Chris Wheeler, OSE/Project Manager, Timothy Jiang, Clinical Reviewer; Frank Pucino, Clinical Reviewer	

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues***	☒ YES Date if known: January 28, 2010 ☐ NO ☐ To be determined Reason:

○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☐ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**: consult issued by ONDQA	☐ Not Applicable ☐ YES ☒ NO ☒ YES ☐ NO ☒ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO
<u>Facility/Microbiology Review</u> (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

<u>CMC Labeling Review</u> (BLAs/BLA supplements only) **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Bob A. Rappaport, MD **21st Century Review Milestones (see attached)** (optional): Mid-cycle mtg, October 15, 2009, Wrap-up meeting, January 14, 2010 **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☒ Standard Review ☐ Priority Review
ACTIONS ITEMS	
☒	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22516	ORIG-1	ELI LILLY AND CO	CYMBALTA

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/s/

AYANNA S AUGUSTUS
11/20/2009

DSI CONSULT: Request for Clinical Inspections

Date: October 7, 2009

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
Susan Leibenhaut
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Anjelina Pokrovnichka, M.D., Clinical Reviewer
Ellen Fields, M.D., Clinical Team Leader

From: Ayanna Augustus

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 22-516
Applicant/ Eli Lilly
Drug Proprietary Name: Cymbalta (duloxetine)
NME : no
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Chronic pain

PDUFA: March 15, 2010
Action Goal Date: March 15, 2010
Inspection Summary Goal Date:

This inspection request is in addition to the current consult for this NDA submitted June 5, 2009. The Applicant submitted an additional Phase 3 trial for review.

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
# 75: Bruce Rankin Avail Clinical Research LLC 860 Peachwood Dr. Deland, FL 32720	HMGC	34	Chronic pain
# 74: Kyle Patrick, D.O. Radiant Research of Phoenix 924 W. Chandler Blvd Chandler, AZ 85225	HMGC	26	Chronic Pain

III. Site Selection/Rationale

The above sites are requested based on the largest proportion of trial participants at domestic study sites.

Domestic Inspections:

Reasons for inspections (please check all that apply):

___X_ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact *Ayanna Augustus* at *301-796-3980 or Anjelina Pokrovnichka* at 301-796-2312.

Concurrence: (as needed)

_____*Ellen Fields*_____ Medical Team Leader
_____*Anjelina Pokrovnichka*_____ Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22516	ORIG-1	ELI LILLY AND CO	CYMBALTA

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/s/

AYANNA S AUGUSTUS
10/08/2009

ELLEN W FIELDS
10/08/2009

DSI CONSULT: Request for Clinical Inspections

Date: June 5, 2009

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46
Joe Salewski., Branch Chief (Acting), GCP2, HFD-47
Name of DSI Primary Reviewer (if known)

Through: Anjelina Pokrovnichka, Medical Officer, DAARP
Ellen Fields, Team Leader, DAARP
Bob Rappaport, Division Director, DAARP

From: Tanya Clayton, DAARP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 22-516
Sponsor/Sponsor contact information (to include phone/email):
Eli Lilly & Company

Drug: Cymbalta (Duloxetine)
NME: No
Standard or Priority: Standard
Study Population < 18 years of age: No
Pediatric exclusivity: No

PDUFA: March 15, 2010
Action Goal Date: March 15, 2010
Inspection Summary Goal Date:

II. Background Information

This supplemental application is an application for an indication for treatment of chronic pain.

Duloxetine is a serotonin and norepinephrine reuptake inhibitor (SNRI) approved in the United States and marketed by Eli Lilly for treatment of major depressive disorder (MDD), diabetic peripheral neuropathic pain (DPNP), generalized anxiety disorder (GAD), and fibromyalgia (FM). Serotonin and norepinephrine are thought to mediate analgesic mechanisms in the brain and spinal cord.

Lilly submitted an application for the management of chronic pain a year ago on May 15, 2008 (NDA 22-333), and subsequently withdrew this application on November 26, 2008.

Four pivotal trials are included in NDA 22-516 to support the safety and efficacy of duloxetine for the treatment of chronic pain. Three of the trials (HMEO, HMEN, and HMEP) were part of the withdrawn NDA 22-333. HMFG is an additional trial in osteoarthritis (OA), submitted with the new application.

(b) (4)

HMEN trial was a double-blind, placebo-controlled, parallel-group trial in patients with chronic low back pain. The duration of the double-blind treatment phase was 13 weeks. At Week 7, non-responders to duloxetine (<30% average pain reduction from baseline) were up-titrated to 120 mg QD. HMEN trial was conducted in 20 study centers in Brazil, France, Germany, the Netherlands, and Mexico.

HMEP trial was a double-blind, placebo-controlled, parallel-group trial in patients with osteoarthritis of the knee. The duration of the double-blind treatment phase was 13 weeks. At Week 7, duloxetine-treated patients were re-randomized to either 60 mg QD or 120 mg QD with the objective of exploring relative efficacy of 120 versus 60.The trial was conducted in 29 study centers in the United States, Puerto Rico, and Romania.

HMEO trial was a double-blind, placebo-controlled, fixed-dose trial in patients with chronic low back pain. The duration of the double-blind treatment phase was 13 weeks. The fixed-dose, parallel design was used to assess group average safety/efficacy profile at 3 dose duloxetine levels – 20 mg QD, 60 mg QD, and 120 mg QD. This trial failed to show evidence of efficacy of duloxetine in CLBP at any dose on all of the efficacy analyses performed by the applicant. The trial was conducted in 31 centers in the United States and Argentina.

HMFG trial was a double-blind, placebo-controlled, parallel-group trial in patients with pain due to osteoarthritis of the knee. The duration of the double-blind treatment phase was 13 weeks. At Week 7, non-responders to duloxetine (<30% average pain reduction from baseline) were up-titrated to 120 mg QD. The trial was conducted in 21 centers in five countries (Canada, Greece, Russia, Sweden and the United States).

III. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
Site # 301 **PI: Dr. Henk Mulder** Ccmo Eudractnr.2006-003484-31 Parnassusplein 5 Den Haag Den Haag 2511 VX Netherlands	F1J-MC-HMEN	64	Treatment of chronic low back pain.
Site # 033 **PI: Dr. Yuri Belenkov** Moscow Medical Academy 6 Building 1 Pirogovskaya Str. Moscow, 119992, Russia	F1J-MC-HMFG	39	Treatment of pain associated with osteoarthritis.
Site # 034 **PI: Dr. Boris Bart** Russian State Medical University 29 Building 2 Miklukho-Maklaya Str. Moscow, 1117485, Russia	F1J-MC-HMFG	15	Treatment of pain associated with osteoarthritis.

IV. Site Selection/Rationale

The above sites are requested primarily based on the largest proportion of trial participants. In addition, Dr. Bart's site demonstrated efficacy results that were more unbalanced between treatment and placebo groups than the other centers in study HMFG.

A foreign site was selected for inspection for HMEN because the trial was conducted in centers all outside the United States.

Domestic Inspections:

Reasons for inspections (please check all that apply):

____ Enrollment of large numbers of study subjects
____ High treatment responders (specify):

____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
___ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
__x__ Other (specify):

- Enrollment of large numbers of study subjects.
- Preliminary efficacy analysis based on the Division's preferred methodology suggested possibly positive outcome for Trial HMEN.
- Study HMEN was conducted only at foreign sites.
- Trial HMFG is the new trial submitted within this application. The applicant claims positive results.
- For HMFG, Site#34, the calculated means and ranges for the change from baseline to week 13 of BPI scores for each treatment group showed that the mean difference is relatively large and the ranges do not overlap.

Five or More Inspection Sites *(delete this if it does not apply)*:
We have requested these sites for inspection (international and/or domestic) because of the following reasons: *state reason(s) and prioritize sites*.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

Concurrence: (as needed)

_____ Medical Reviewer

_____ Medical Team Leader

_____ Director, Division Director (for foreign inspection requests only)

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/s/

Ellen Fields
6/18/2009 01:29:14 PM

Bob Rappaport
6/18/2009 05:54:31 PM